Chapter 11
New Peritoneal Dialysis Solutions and Solutions on the Horizon

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This chapter discusses 1) the effects of alterations in electrolytes, 2) amino acids, 3) icodextrin, and 4) biocompatible peritoneal dialysis (PD) solutions.

Effects of Alterations in Electrolytes

Magnesium

Magnesium is an important cation involved in several enzymatic reactions. The serum concentration of magnesium in dialysis patients depends on dietary intake and on the concentration of the cation in the dialysis solution. Normal values of total serum magnesium range from 0.65 to 0.98 mmol/L, while its diffusible fraction is about 55–60% of the total. Commercially available continuous ambulatory peritoneal dialysis (CAPD) solutions contain 0.25–0.75 mmol/L of magnesium. In such conditions, when 0.75 mmol/L magnesium and 1.5% glucose solutions are used in CAPD, a slight magnesium uptake from the dialysis solution usually occurs by diffusive gradient [1]. Kwong et al., however, have reported a negative dialytic balance with the same solution [2].

When ultrafiltration is increased by a 4.25% dextrose solution, convective removal counteracts diffusive uptake, yielding a negative magnesium mass transport in most patients [1]. Not only is peritoneal transport of magnesium influenced by diffusion gradients and ultrafiltration rates, but also by dwell time and peritoneal permeability because of the large hydrated radius of the molecule [1].

In most papers [3–6] the use of 0.75 mmol/L magnesium solutions resulted in elevated levels of magnesium in the serum. Hypermagnesemia is a common finding in dialysis patients [7]. While it is almost impossible to show abnormalities related to modestly elevated magnesium concentrations, when serum magnesium increases above 2 mmol/L symptoms of neuromuscular and cardiovascular toxicity are present [8]. Controversial reports concerning beneficial or deleterious effects of hypermagnesemia in dialysis patients have been published. Potential harmful effects include pruritus [9], altered nerve conduction velocity [10], and contribution to osteomalacic renal osteodystrophy by inhibiting bone remodeling [11]. Other authors pointed out that hypermagnesemia does not result in any clinical complication and, on the contrary, a protective role on soft tissue calcifications has been suggested [12]. A suppression of parathyroid hormone (PTH) [13] has also been suggested. This latter effect has recently been hypothesized to have a pathogenetic role in adynamic bone disease [14]. Despite such frequent hypermagnesemia, the muscle content of magnesium is generally not altered [15]. Therefore, the relationship of serum magnesium to intracellular magnesium concentration and total body magnesium in CAPD patients is unclear. Dietary magnesium intake is a function of protein intake. On the other hand, magnesium removal with standard 0.75 mmol/L magnesium solutions is negligible. In spite of these observations, CAPD patients do not display a continuous increase of serum magnesium levels, and stool magnesium losses may play a regulatory function [16].

To achieve a correct balance, Nolph et al. suggested lowering dialysate magnesium to 0.25 mmol/L [4]. The use of this solution did not cause hypomagnesemia, and most patients experienced a normalization of magnesium serum levels [4, 17]. In a more recent report, however, 64% of the studied CAPD population using the low magnesium containing CAPD fluid showed a reduction in serum magnesium levels [18]. Since hypomagnesemia has been associated with cardiac arrhythmias [19, 20] and various electrocardiographic abnormalities [21], serum magnesium levels should be monitored during treatment with these solutions. In addition, the use of an ion-selective electrode for

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the measurement of the ionized magnesium, the active fraction of this cation, has shown that the correlation between total serum and ionized magnesium is less strong in CAPD patients than in normal subjects due to hypoalbuminemia and the increased complexed fraction of magnesium often present in dialysis patients [22]. This could imply that significant magnesium depletion can be present despite a normal serum value [23].

The use of lower or zero magnesium dialysate has also been investigated to permit oral treatment of hyperphosphatemia with magnesium salts as a calcium-free phosphate binder [24]. This, however, frequently results in a laxative effect, requiring careful monitoring of compliance to therapy and serum magnesium levels [25, 26].

Calcium

In the past, peritoneal dialysis fluids (PDF) contained 1.75 mmol/L of calcium. This concentration was chosen in order to ensure a positive calcium balance since, in uremic patients, the active vitamin D deficit leads to a reduction in calcium absorption from the gastrointestinal tract. In this condition serum calcium concentration is low, PTH is high, and a high-turnover bone disease often occurs. In addition, PTH was considered one of the most harmful "uremic toxins" because of its deleterious effects on several organs and functions.

While a negative balance may result from the use of 1.5 mmo/L dialysate calcium [27], kinetic studies suggest that CAPD solutions with 1.75 mmol/L of calcium (three exchanges with 1.5% glucose and one exchange with 4.25% glucose) generally lead to peritoneal calcium absorption and rapidly normalize total and ionized calcium serum levels [1–3, 28]. This was suggested to be beneficial in order to prevent progression of uremic osteodystrophy and calcium losses from the bone [6–29]. However, clinical studies did not confirm such a positive effect [27, 30–31].

Since normal serum concentration of diffusible ionized calcium ranges from 1.15 to 1.29 mmol/L, calcium is absorbed from PDF or lost into PDF depending on diffusive gradient direction [1]. In CAPD solutions, 30% of calcium is not ionized being "chelated" by lactate [2]. Ionized calcium probably crosses the peritoneum faster than chelated calcium. As a consequence, ionized calcium gradient is rapidly dissipated. The rapid increase in dialysate pH further contributes to this phenomenon decreasing calcium ionization in the solution [2]. A significant correlation between positive calcium balance and dialysate/serum gradient for ionized calcium has been found by using 1.75 mmol/L calcium solutions [2]. Blumenkrantz et al. have also reported that net dialytic calcium uptake inversely correlates with total serum calcium [32]. When ultrafiltration increases in hypertonic exchanges, calcium uptake tends to decrease [1] or even to become negative [2, 28]. Different rates of ultrafiltration may help to explain discrepancies among different studies. Convective removal counterbalances diffusive uptake and decreases dialysate/serum gradient because of a dilution effect [33].

Overall calcium mass-balance is also affected by gastrointestinal absorption. In CAPD patients, an empirical relationship has been found between dietary intake and gastrointestinal absorption [32]. One study found that 720 mg/day of dietary calcium intake resulted in an estimated average gastrointestinal absorption of 25 mg [32].

When new attention was paid toward the deleterious effects of the high phosphate serum levels often encountered in dialyzed patients, and the danger of aluminum toxicity contained in the aluminum-containing phosphate binders was recognized [34–37] (osteomalacia and encephalopathy), the calcium salts of carbonate and acetate were introduced as phosphate binders. Block et al. [38] have recently pointed out that hyperphosphatemia but also moderate to severe hyperparathyroidism and hypercalcemia are associated not only with bone disease but also with cardiovascular disease and greatly affects mortality in dialyzed patients. Calcium-containing phosphate binders were aimed to both reduce serum phosphate levels and hyperparathyroidism through an increase in serum calcium levels. However, if oral calcium supplementations are administered as phosphate binders, significantly greater amounts of calcium are absorbed from gastrointestinal tract. Assuming a daily phosphate intake of 1,000 mg in CAPD patients [39], 70% of this should be bound in the intestinal tract to maintain the balance [28]. This goal can be achieved with 6.25 g of calcium carbonate supplementation (2,500 mg of elemental calcium), which leads to an average gastrointestinal calcium absorption of 700 mg/day [40, 41]. Hence, in a standard patient, total calcium absorption from the diet and calcium carbonate is approximately 725 mg/day. In such conditions, a large number of patients may encounter an increased risk of hypercalcemia and soft tissue calcification [42].

A solution to this puzzle has been found by using a lower dialysate calcium concentration. This approach has been suggested to avoid the risk of calcium carbonate–related hypercalcemia [1]. Martis et al. [43] have calculated on theoretical bases that a calcium concentration of 1.25 mmol/L in peritoneal fluid would lead to a calcium removal of 160 mg/day when serum ionized calcium is 1.3 mmol/L and to a greater removal in the case of hypercalcemia. In a prospective clinical study, Hutchison et al. [17] have demonstrated that a 1.25 mmol/L calcium dialysate allowed the administration of larger doses of calcium carbonate with good control of serum phosphate, and maintained serum

ionized calcium near to the upper limit of the normal range. Parathyroid hormone was suppressed in the majority of patients and bone histology improved. Similar results have been achieved in a large multicentric study in which 1 mmol/L calcium solution has been used and low doses of vitamin D and calcium carbonate as phosphate binders have been orally supplemented [44]. However, in the long term, a great percentage of patients with low calcium dialysis fluid (23%) as compared to patients with 1.75 mmol/L calcium dialysis fluid (10%) experienced worsening of the preexisting hyperparathyroidism [45].

Low calcium PD fluids have been extensively studied by several investigators and the results confirm the benefit of this approach on uremic osteodystrophy [46–50]. Long-term usage of lower calcium dialysate by large numbers of patients raises the question of safety in cases of poor compliance to oral calcium carbonate supplementation. In 12 patient treated with 1.5% glucose and 1.25 mmol/L calcium solution, a net gain of calcium was demonstrated when the serum ionized calcium level was less than 1.25 mmol/L. This observation seems to prove that a very low risk of hypocalcemia is present in these patients [17]. However, there is a tendency to lose calcium regardless the serum-ionized calcium in patients treated with 4.25% glucose and low calcium solutions. Since a rapid exacerbation of hyperparathyroidism in some patients converted to low calcium dialysate without adequate oral calcium supplementation has been documented [51] in CAPD patients using two or more hypertonic bags per day and a low calcium solution, a careful surveillance of the mineral metabolism is needed.

In the last decade, the prevalence of type of bone lesions in PD patients has changed and adynamic bone disease has been increasingly recognized [52]. The term "adynamic bone disease" indicates a reduced activity of the physiologic process of bone remodeling with reduced synthesis of bone matrix, osteoblastic and osteoclastic activity, and a lack of osteoid accumulation. In this condition, patients are predisposed to the risk of poor healing of microfractures and to an increased incidence of fractures. In addition, since the calcium buffering effect of bone is diminished [53–55], patients with a positive calcium balance from calcium-containing phosphate binders and/or high-calcium PDF can be exposed to frequent episodes of hypercalcemia with calcium deposition in the vascular bed and myocardium that increase cardiovascular mortality [56]. In a large number of bone biopsies in an unselected end-stage renal disease (ESRD) population in Toronto, the percentage of adynamic bone disease was 61% in PD patients as compared with 36% in HD patients [57]. More recent observations confirmed these data (63% of adynamic bone disease in PD patients) [58].

The etiology of adynamic bone disease is unknown but several risk factors have been suggested [59–61], the most important probably being the oversuppression of PTH secretion and/or the lack of physiologic fluctuations in secretion. High calcium serum levels, positive calcium balance from calcium-containing phosphate binders, or high calcium PDF and vitamin D administration are the main factors involved in the PTH oversuppression. The role of the positive calcium balance in this condition is confirmed by the increase of serum PTH levels in patients treated with low calcium PDF and switched from calcium-containing phosphate binders to non-calcium-containing phosphate binders such as sevelamer [52].

The concerns about adynamic bone disease have changed the previous views on maintaining calcium serum levels of PD patients at the highest value of the normal range in order to reduce PTH secretion. The Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines [62] recommend PTH values from 150 to 300 pg/mL and a serum calcium $<$9.5 mg/dL. Recognition of the high prevalence of the adynamic bone disease in PD patients and the understanding of its supposed pathophysiology have added new indications to the use of low calcium PDF so that the formulation containing 1.25 and 1 mmol/L are now suggested by guidelines on PD.

Several studies have been performed comparing the effect on bone diseases of the high and low calcium PDF in adynamic bone disease PD patients. In the study of Sanchez et al. [63], no significant histological changes were recorded in the low calcium group (1.25 mmol/L) as compared with standard 1.75 mmol/L calcium PDF. As expected, PTH increased in the study group and calcium-containing phosphate binder medication was increased while no changes in serum calcium and phosphate levels were recorded.

A recent randomized study [64] comparing the effects of standard versus low calcium (1 mmol/L) PDF for an extended period of 16 months in CAPD patients with biopsy-proven adynamic bone disease showed in the study group an increase in bone formation rate to normal range being suppressed at baseline and no changes in the control group. Serum-ionized calcium significantly decreased despite an increase in calcium carbonate supplementation and PTH rose of about 300% in the low-calcium PDF group. Again, no changes in the standard calcium PDF were observed. Bone mineral content did not decrease during the study in either group, demonstrating no calcium loss from bone. In addition, in the study group hypercalcemic episodes decreased significantly while asymptomatic hypocalcemia occurred infrequently. Some patients in the low-calcium PDF did not change the bone histology due to an insufficient bone formation rate increase. The authors hypothesized that the relatively high doses of calcium carbonate were still able to maintain a positive calcium balance and the new calcium-free phosphate binders could add a further benefit in this condition.

The commercially available solutions for automated peritoneal dialysis treatments are substantially similar to those for CAPD. Andersen [65] reported that a positive calcium transfer from dialysis fluid can be obtained with a 2.16 mmol/L calcium concentration in dialysate both during 1.5% and 4% glucose 30 min dwell-time exchanges, while in automated peritoneal dialysis, the low-calcium dialysis solution (1.25 mmol/L) could result in a negative calcium balance [66]. Although there are no specific studies of calcium mass balance and calcium mass transfer in automated peritoneal dialysis (APD), it seems reasonable that, since larger volumes of fluid are utilized with greater ultrafiltration and shorter dwell times, the calcium balance would be negative or at least less positive than in CAPD [67]. This implies that a bigger dose of calcium containing phosphate binders and vitamin D supplementation could be used with less risk of hypercalcemia and PTH suppression. The major mineral metabolism problem could be the hyperparathyroidism. The new calcium mimetics or vitamin D analogues could be of value for treating this condition.

Low Sodium

Most commercially available dialysis solutions have a sodium concentration of 132–134 mmol/L, which is an average of about 5 mmol/L lower than the plasma sodium concentration. Because of this small concentration gradient, the transport of sodium is mainly determined by convection [68]. The magnitude of net convective transport is dependent on the balance between transcapillary ultrafiltration and the peritoneal absorption of the dialysate.

The diffusion of sodium can be increased by lowering the sodium concentration of the dialysis fluid. However, when this is done without raising the dialysate glucose concentration, keeping the osmolality constant, the increased diffusional transport is counteracted by a decreased removal by convection. [69]. The diffusion of sodium is dependent on the concentration gradient between plasma and dialysate, and on the mass transfer area coefficient. The latter has yielded values that are dependent on the experimental setting in which it was calculated. Using a conventional 3.86% glucose-based solution, an average value of 4 mL/mm has been reported during a period of isovolemia [70]. Values of 7–8 mL/min have been found using experimental dialysis solutions with a sodium concentration of 102–105 mmol/L [71, 72].

Single dwell studies have shown that sodium removal can be increased three-fold when a dialysate sodium concentration of 100 mmol/L is used [71]. This was confirmed in the only clinical study in which six overhydrated patients were treated with such a solution once daily for seven consecutive days [73]. Other significant effects included decreases of body weight and blood pressure. Clinical studies performed after these initial cases have only published in abstract form. Low or ultralow sodium-containing dialyis solutions have never been produced on a large scale and are currently not available.

Amino Acids

A high percentage of patients treated with peritoneal dialysis present different degrees of malnutrition [74]. Since CAPD patients absorb a substantial amount of glucose from the peritoneal dialysis solution and many of them become obese [75], it seems that protein rather than caloric deficit is the major problem for these patients. Continuous losses of amino acids (3–4 g/day) and proteins (8–15 g/day) into dialysate greatly contribute to this nutritional derangement [75, 76].

In the late 1960s, Gjessing suggested supplementing peritoneal dialysis solutions with a mixture of amino acids to correct serum amino acid abnormalities and to prevent obligate protein losses with dialysate [77]. More than 10 years later, Oreopoulos et al. proposed an amino acid solution in peritoneal dialysis both for nutritional supplementation and as an alternative to glucose as the osmotic agent. Experiments in a uremic rabbit model [78] and in peritoneal dialysis patients [79, 80] underlined the advantages of substituting glucose in the solution and improving nutritional support.

Osmotic Efficacy

Molecular weights of different amino acids range from 75 to 214 daltons. Since amino acid mixtures for PD usually contain a higher proportion of small-molecular-weight compounds, the average molecular weight represented in these solutions is approximately 100 daltons [81], which is lower than that of glucose. Nevertheless, the absorption rate of amino acids is not significantly faster than that of glucose. Since, at the fresh dialysis solution pH, some amino acids

are electrically charged, the hydration shell increases the relative Einstein-Stokes radius of the molecules. As a consequence, diffusion coefficients are smaller in comparison to uncharged molecules with equivalent molecular weight, and absorption velocity is reduced. It has been demonstrated that the D/P ratio for creatinine is near to that of glutamine (a near neutrally charged amino acid with almost the same molecular weight) but significantly higher than that of glutamic acid (negatively charged) and of lysine (positively charged), both with the same molecular weight of creatinine [82].

Several studies have been performed to evaluate the ultrafiltration capacity of amino acid solutions. A 2% amino acid solution was compared to a 4.25% glucose solution in an acute study on 6-h exchanges [80]. The two solutions induced equivalent amounts of ultrafiltration and similar amounts of urea, creatinine, and potassium removal. The initial dialysate osmolality was similar for the two solutions and similar dialysate osmolality changes during dwell time were observed. At the end of the exchange, 90% of the administered amino acids were absorbed. Later, the same group [83] reported a short-term study in which the ultrafiltration obtained with a 1% amino acid solution (osmolality 364 mmOsm/kg) was intermediate between that of 1.5% (osmolality 346 mmOsm/kg) and 2.5% (396 mmOsm/kg) standard glucose solution. Goodship et al. confirmed the observation of smaller but not statistically different ultrafiltrate volumes, comparing a 1% amino acid solution with a 1.5% glucose solution [84].

A comparison of ultrafiltration profiles and solute mass transfer between a 4.25% glucose (478 mmOsm/kg) and a 2.76% amino acid (501 mmOsm/kg) solution showed that intraperitoneal volume profiles were equal during the first 180 min of dwell. Later, the volume of amino acid solution tended to decrease more rapidly than that of glucose solution, leading to a nonsignificant decrease in net ultrafiltration at the end of the 6-h dwell time exchange [85]. The diffusive mass transport coefficient tended to be higher with amino acid solutions, but the difference was not statistically significant . Young et al. [86] studied ultrafiltration and D/P ratios of several proteins in an 8-h dwell time exchange using a 1% amino acid solution in comparison with 1.5% glucose standard solution. Volumes of dialysate at the end of the exchanges were significantly less after amino acid exchanges, although the osmolality decreased comparably during the dwell time. At the end of the study period (12 weeks), amino acid absorption and protein losses were increased as compared to the beginning of the study. The clearances of the studied proteins expressed as D/P ratios showed a 18–34% increase, respectively, at the beginning of the amino acid use and after 12 weeks. D/P ratios for creatinine showed a 7–10% increase, respectively, while no differences were observed for urea. The increase of the peritoneal permeability during the use of amino acid–based solution was attributed to an activation of complement by amino acids or their metabolites to produce C5a [87] and the generation of prostaglandin E2 [88]. The peritoneal permeability increase was reversed when standard glucose solutions were resumed [86].

Douma et al. [89] have reported a study on the peritoneal membrane permeability when a 1.1% amino acid solution is used: the mass transfer area coefficients of low-molecular-weight solutes (creatinine, urea, and urate) were significantly greater with amino acid solution compared to glucose solution. The clearances of the macromolecules were also greater with the amino acid solution, but the increase of albumin and IgG clearances was small and not significant. The transcapillary ultrafiltration rate was higher during the amino acid treatment, but no significant difference in net ultrafiltration was found. These data indicated a vasoactive effect of the amino acid solution: the increased peritoneal blood flow and the effective peritoneal surface area were probably caused by vasodilation. This was not associated with changes in intrinsic permeability to macromolecules or increased protein loss. This study also demonstrated that these effects were not due to nitric oxide activity (L-arginine contained in the amino acid solution could serve as a substrate for nitric oxide synthesis) nor to the peritoneal release of prostaglandins.

Despite the contradictory results of kinetic studies, in clinical practice amino acid solutions deliver ultrafiltration and small molecule clearances equivalent to those achieved with 1.36% glucose solutions. The differences among various studies probably reflect the difference in concentration and composition of amino acids in the employed solutions. The osmotic power produced by different solutions is not only expressed by the osmolality, calculated or measured, but also depends on the degree of absorption and metabolization of each amino acid [90].

Nutritional Efficacy

Nutritional value, changes in serum amino acid profile, amino acid absorption, and the effects on lipids and glucose metabolism of CAPD amino acid solutions have been evaluated in clinical studies. During the 30 years of experience and attempts to find out the best composition for the amino acid solution, several amino acid formulations of the CAPD solutions have been proposed and tested. Table 11.1 reports the amino acid composition of some of the most used. Clinical results were often conflicting because different amino acid composition solutions were used, different parameters were taken into account as markers for nutrition, different CAPD population were studied (malnourished

Table 11.1 Amino acid composition (mg/dL) of different solutions (see references in the text)

Category	Amino acid	Solution A	Solution B	Solution C	Solution D
EBCAA	Valine	46	126	139.3	123
EBCAA	Leucine	62	92	101.9	85
EBCAA	Isoleucine	48	77	84.9	70
EAA	Threonine	42	59	64.5	54
EAA	Tyrosine	4	6	30	27
EAA	Phenylalanine	62	75	57	47
EAA	Lysine	58	86	76	55
EAA	Hystidine	44	65	71.4	59
EAA	Tryptophan	18	25	27	23
EAA	Methionine	58	77	84.9	36
NEAA	Arginine	104	97	107.1	68
NEAA	Serine	–	46	50.9	55
NEAA	Proline	42	54	59.5	49
NEAA	Glycine	213	46	50.9	42
NEAA	Alanine	213	86	95.1	77
NEAA	Aspartic acid	–	–	–	65
NEAA	Glutamic acid	–	–	–	65

EBCA: Essential branch-chained amino acid; EAA: Essential amino acid; NEAA: Nonessential amino acid

versus nonmalnourished, different caloric intake), different CAPD schedules were used (amino acid solution used in the overnight exchange versus in exchanges close to a meal).

The clinical results with solution A in Table 11.1 were rather discouraging, showing insufficient effects on nutritional parameters and some unwanted effects such as increased levels of blood urea nitrogen (BUN) (with symptoms of uremia), loss of appetite, and moderate to severe metabolic acidosis [83, 91–93]. The authors concluded that the amino acid formulation, the timing of administration, the patients' low caloric intake, or the patients' sufficient nutritional state could be responsible for the ineffectiveness of the amino acid solution and that the intraperitoneal supply of amino acids was probably used as a source of energy [94].

Following the these experiences, a new 1% amino acid solution was proposed and tested (solution B in Table 11.1). This solution was designed specifically for patients with renal insufficiency and its related amino acid derangements [95]. Thus, the essential amino acid proportion was increased and the lactate concentration was increased to 35 mmol/L.

The studies using the improved 1% amino acid solution demonstrated more beneficial effects than the previous solution in patients with signs of protein malnutrition and low dietary protein intake. Some nutritional parameters such as serum transferrin [96, 97], albumin [98], estimated nitrogen balance (99–100), and serum amino acid profile [93, 94] improved during the study. In all these reports, lipid metabolism improved, BUN increased, and acidosis remained a commonly concern. This was most likely due to the acid load delivered by salts of basic amino acids (lysine hydrochloride) and that arising from metabolism of sulfur amino acids to sulfate (methionine) [101].

In order to further improve the clinical efficacy, a new formulation of the amino acid solution has been proposed and tested (solution C in Table 11.1). Essential amino acid concentrations were increased as well as lactate concentration (from 35 to 40 mmol/L). Total amino acid concentration was increased to 1.1% in order to provide the same osmotic effect as the 1.5% standard glucose solution. This is the formulation now commercially available. A short-term crossover multicentric study in CAPD patients with signs of protein malnutrition has been performed [102]. The nitrogen balance, serum transferrin, and total protein increased in 19 malnourished patients using one or two 1.1% amino acid solution for 20 days. Dietary protein intake of 0.8 g/kg/day and caloric intake of 25–30 kcal/kg/day was prescribed to all patients. Because of the amino acid absorption from dialysis fluid, a total protein intake of 1.1–1.3 g/kg/day was achieved in all patients. Protein anabolism was positive, as directly determined from ^{15}N-glycine studies and indirectly from the plasma phosphate and potassium decrease. The amino acid pattern in plasma tended toward the normal range during the treatment phase and serum triglycerides and HDL cholesterol increased. Plasma total CO_2 significantly decreased, showing a tendency toward a metabolic acidosis mainly in patients treated with two exchanges per day of this solution.

A clinical evaluation of this amino acid solution was performed in a second study [103]. This was a 3-month prospective crossover study in 15 stable CAPD patients not necessarily malnourished. Only one exchange with amino acid was prescribed at lunchtime to couple amino acid absorption with energy intake. Serum albumin and transferrin

significantly improved both in patients with and without malnutrition. Plasma amino acid profile and total proteins did not change. Plasma bicarbonate levels also remained stable.

A prospective randomized study was also performed in order to compare the nutritional effects of the 1.1% amino acid solution with the conventional glucose solution in 54 malnourished patients [104]. After an initial significant increase in serum albumin, transferrin, prealbumin, and total protein, after 3 months of treatment these parameters did not achieve the statistical significance as compared with those of the 51 patients in the control group. However, in the tertile with the lowest albumin levels at the baseline, serum albumin and prealbumin remained significantly increased. In the tertile with the highest albumin levels at the baseline, the mid-arm muscle circumference increased significantly after 3 months of treatment. In the whole population treated with the amino acid solution, circulating insulin-like growth factor 1 (IGF-1) increased, while it slightly decreased in the control group.

In an acute study the amount of amino acids delivered by this amino acid solution was quantified [105]. It has been shown that the gain of amino acid during one exchange largely exceeded the daily losses of amino acid and proteins. This effect was independent of the peritoneal membrane transport type. Skeletal muscle amino acid uptake was increased after 6 weeks use of this solution in 10 CAPD patient [106] and, in an acute study using the ^{3}H-phenylalanine kinetics as indicator, muscle protein synthesis increased by 20% [107].

A short-term use of amino acid solution was also effective in improving net protein balance and converting nitrogen balance from negative to positive in patients on automated PD [108]. Other studies could not demonstrate an improvement in nutritional parameters in well-nourished CAPD patients treated with 1.1% amino acid solution [109, 110]. The longest experience with this amino acid solution was performed by Li et al. [111]. Sixty malnourished Chinese patients were randomized to receive either the amino acid or the conventional solution for 3 years. Normalized protein equivalent of nitrogen appearance (nPNA) and dietary protein intake increased while triglycerides decreased in the study group, Albumin and cholesterol remained stable in the treated group and decreased in the control group. No differences were recorded in mortality, hospitalization, drop out, and composite nutritional index between groups. The last report on the 1.1% amino acid solution is an observational study in 46 malnourished Korean patients [112]. After 1 year of treatment, mean serum value of blood urea, creatinine, lean body mass, nPNA, serum IGF-1 level, back lift strength and SGA score increased significantly. The other studied nutritional parameters (albumin, hand grip strength, anthropometry, and dietary intake) did not change and serum bicarbonate statistically decreased.

In conclusion, in malnourished CAPD patients a dialysis solution with a more appropriate amino acid composition may improve their protein nutrition and metabolic status. However, increased BUN levels and the tendency toward acidosis remain problems to be solved. The last point has been addressed by Jones et al. [113]. They tested a modified amino acid solution formulation (solution D in Table 11.1) in which acidogenetic amino acid concentrations (lysine, arginine ,and methionine) were reduced in comparison with the 1% amino acid solution (solution C in Table 11.1). In addition, aspartic and glutamic acids, two dicarboxylic acids that generate alkaline equivalents during their metabolism, were added. A substantially better acid-base status was achieved during the treatment with the modified amino acid solution as compared to the conventional amino acid solution.

Icodextrin

History

Icodextrin is the only high-molecular-weight osmotic agent that has been approved for use in peritoneal dialysis patients. The name icodextrin is derived from the Greek word *icosa* (“twenty”) and the chemical name *dextrin*, describing a glucose polymer obtained by the partial hydrolysis of starch with a molecular weight of about 20,000 dalton [114]. Dextrins are polymers in which the glucose molecules are linked at the α1–4 position. This is different from dextran, where α1–6 linkages are present. The difference in the linkages is crucial in relation to the manner in which these polymers behave in the body. There are a number of enzymes that can attach themselves to the α1–4 polymer and break this bond, producing oligosaccharides, maltose, and eventually glucose. This is different from the α1–6 bond, which is more resistant to enzymatic cleavage.

Icodextrin as used for PD is prepared by hydrolysis of corn (maize) starch and purified enzymatically to maltodextrin. Using a number of filtration steps, the low-molecular-weight fractions are removed. This results in a dextrin preparation with a molecular weight range from 1,640–45,000 daltons. The average molecular weight is 16,800 daltons, and >90% of the bonds are of the α1–4 type.

The first clinical study using a single 6- and 12-h dwell with a 5% icodextrin solution was published in 1987 [115]. A comparison with a 1.36% glucose solution showed that net ultrafiltration at the end of the 6-h exchanges was greater

with the polymer, despite the lower osmolality of the polymer solution. For glucose, increasing the exchange time to 12 h led to absorption of the intraperitoneal volume in all patients, resulting in negative ultrafiltration; with the glucose polymer solution, ultrafiltration continued throughout a 12-h exchange. The absorption of the polymer averaged 14.4% of the instilled quantity after 6 h and 28.1% after 12 h, probably by uptake into the lymphatic system. Because α1–4 bonds are degraded by circulating α-amylase, the absorption causes a rise of the plasma maltose concentration of 0.79 mmol/L (about 0.3 g/L) after 12 h [115].

This initial observation resulted in a number of issues: 1) the use of the glucose polymer during the long exchange, 2) restriction of its use to one exchange per 24 h to prevent extensive maltose accumulation and allow peritoneal removal of maltose during the other exchanges, and 3) the concept of its action by colloid osmosis, similar to that of albumin [116]. This process is based upon the principle that fluid flow across a membrane permeable to small solutes occurs in the direction of relative excess of impermeable large solutes, rather than along the osmolality gradient.

The final preparation used for subsequent studies consists of a 7.5% icodextrin solution, lactate-buffered, with an osmolality of 285 mOsm/kg water. Its composition is given in Table 11.2.

Pathophysiology

The concept of colloid osmosis, leading to fluid transport mainly through the so-called small pores, has been confirmed by showing the absence of sodium sieving [117]. Using dextran 70 as a volume marker, the intraperitoneal volume showed a linear increase during at least 8 h [118], as shown in Fig. 11.1. The absorption of icodextrin averaged 21% after a 4-h dwell, suggesting uptake into the lymphatics similar to that of other intraperitoneally administered macromolecules [117]. The high and persistent fluid flux across the small pore system causes an increase in convective transport, leading, for instance, to an increase in the peritoneal transport of beta-2-microglobulin [117, 119].

Many studies have found a relationship between peritoneal solute transport rates and the efficacy of ultrafiltration on icodextrin [117, 118, 120]. The higher the D/P ratios or mass transfer area coefficients, the better the net ultrafiltration. The explanation is obvious: high D/P ratios suggest a large peritoneal vascular surface area, so more small pores are available for fluid transport. This relationship has been supported by the results of computer simulations [121] and by observations during peritonitis where more, instead of less, ultrafiltration was found [122, 123]. It appeared possible to adequately predict fluid kinetics on icodextrin with a modified three-pore model [124].

Kinetic studies with icodextrin in rats suggested intraperitoneal breakdown of icodextrin during the dwell, both in a stable situation and during peritonitis [125, 126]. However, this could not be confirmed in PD patients [127] and is probably due to the extremely high amylase concentrations in rats. This makes the rat unsuitable for performing kinetics studies with icodextrin.

The presence of a fast peritoneal transport status, reflecting a large peritoneal surface area, leads to a reduction in ultrafiltration with glucose-based solutions due to a high diffusion rate of glucose. As discussed above, icodextrin is especially potent in this situation, because the colloid osmotic pressure gradient remains stable for several hours. This has led to the use of icodextrin as salvage therapy in chronic PD patients with ultrafiltration failure. Some retrospective studies reported that icodextrin enabled patients who would otherwise have been transferred to hemodialysis to continue PD [128, 129]. This has been confirmed in a prospective study [130].

Table 11.2 Composition of 7.5% icodextrin compared to a 3.86% glucose solution

	Glucose	Icodextrin
Na + (mmol/L)	132	133
Ca++ (mmol/L)	1.25/1.75	1.75
Mg++ (mmol/L)	0.25/0.75	0.25
Cl– (mmol/L)	102	97
Lactate (mmol/L)	35/40	40
Glucose (g/L)	38.6	0
Dextrin (g/L)	0	75
Osmolarity (mOsmol/L)	486	285
pH	5.5	5.8

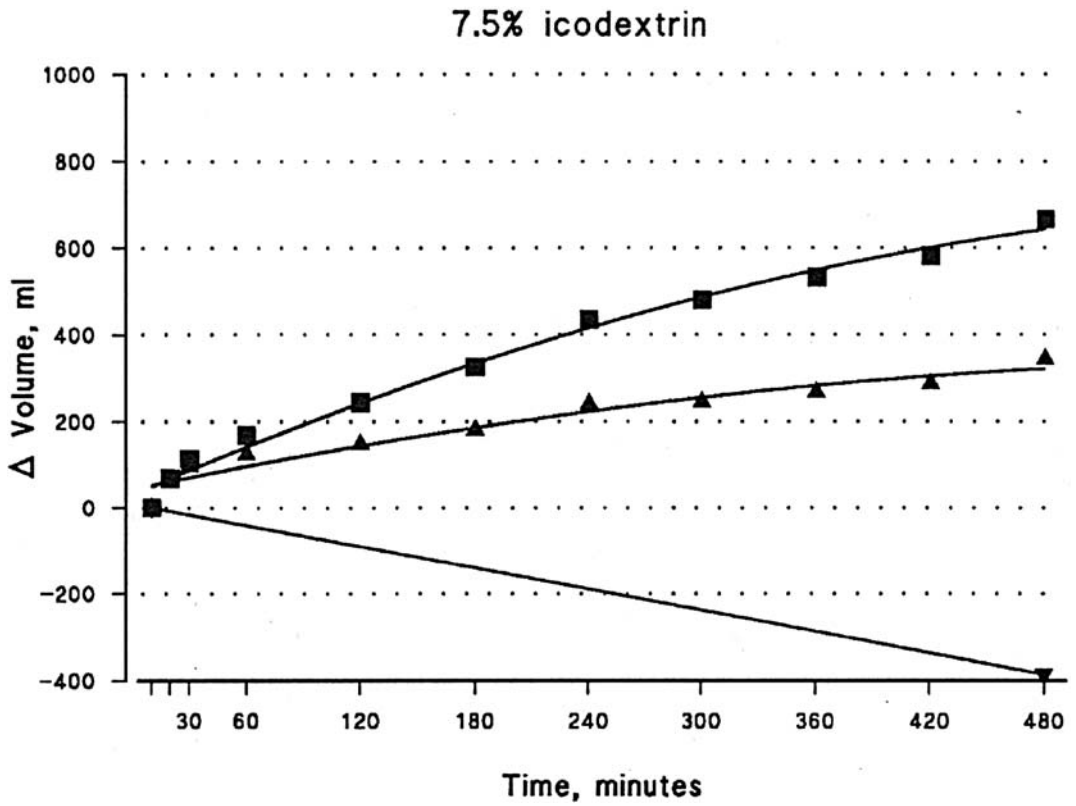

Fig. 11.1 The time course of peritoneal fluid kinetics during an 8-hour dialysis dwell using 7.5% icodextrin. The upper line represents the volume increase due to transcapillary ultrafiltration, the lower line represents the decrease in intraperitoneal volume caused by the effective lymphatic absorption rate. The middle line shows the almost linear increase in the in situ intraperitoneal volume. Taken from ref [118] with permission of the author and of Blackwell Scientific Publishers

Biocompatibility of Icodextrin

The following factors can contribute to the bioincompatibility of PD solutions: acidity, buffer, hyperosmolality, glucose, and glucose degradation products (GDP). Icodextrin contains no glucose, isosmolar, and the concentrations of GDPs are lower than those in a 1.36% glucose solution [131]. The first in vitro study of the biocompatibility of icodextrin showed no improvement compared to glucose-based solutions [132]. However, at neutral pH the secretion of interleukin (IL)-6 by monocytes was superior to that after exposure to a 1.5% glucose-based solution [133]. Improved phagocytosis by peripheral polymorph nuclear cells and monocytes has been described after stimulation with icodextrin compared to standard solutions [134]. Ex vivo studies have shown improved phagocytosis of peritoneal macrophages when isolated from icodextrin effluent, compared to those from glucose effluent [135]. Similarly, the proliferation capacity of mesothelial cells on icodextrin was better [136]. The cancer antigen 125 (CA125) appearance rate in peritoneal effluent probably reflects mesothelial cell mass and is used as an in vivo biocompatibility marker for new dialysis solutions [137]. This parameter was not influenced by acute [138] or chronic treatment with icodextrin [139], probably because it is always combined with other osmotic agents for the short dwells.

Randomized Controlled Trials with Icodextrin

Two large randomized controlled trials (RCT) have been published on the efficacy and safety of icodextrin in prevalent PD patients [140, 141]. The MIDAS study, performed in the United Kingdom, was done in CAPD patients and had a follow-up of 6 months [140]. Icodextrin for the long dwell was compared with glucose. Icodextrin showed superior ultrafiltration after an 8 h dwell than 1.36% glucose and similar to 3.86% glucose. Mean serum sodium decreased from 140 to 136 mmol/L, probably because of slightly increased serum maltose levels that remained stable throughout the

study. An overall CAPD-related symptom score was better for icodextrin, compared to glucose. The RCT performed in the United States comprised CAPD and APD patients, and had a follow-up of 1 year [141]. The results were similar to those of the MIDAS study. Mean net ultrafiltration was higher on icodextrin compared to 2.5% dextrose for the long dwell. Body weight was stable on icodextrin but increased in the 2.5% glucose group and less icodextrin than glucose patients reported edema. The beneficial results on long dwell ultrafiltration in APD were similar to those described in other studies [142, 143].

The effects of icodextrin on net ultrafiltration, especially in patients with fast transport rates of low-molecular-weight solutions (see the section on pathophysiology) have prompted more RCTs in this patient group. A multicenter RCT in APD patients with a fast average or fast transport status showed superiority of 7.5% icodextrin for the long dwell compared to 4.25% dextrose [144]. Another double-blind RCT in CAPD and APD patients with fast average or fast transport status and a urine production <750 mL/24 h, comparing 7.5% icodextrin with 2.2.7% glucose for the long dwell, showed a decrease in body weight, total body water, and extracellular fluid in the icodextrin group during a follow-up of 6 months [145]. The beneficial effects of icodextrin on volume status were also found by Konings et al., who additionally reported a reduction of left ventricular mass, assessed by echocardiography [146].

General Effects and Side Effect of Icodextrin

The better control of volume status achieved with icodextrin could lead to better control of blood pressure. This was indeed found in one study [147], but could not be confirmed in another [145]. A beneficial effect on lipids has also been reported [148], but this could also not be confirmed in a larger study [145]. Improvement of diabetic control has been reported as assessed from Hb1Ac levels and insulin requirements [149]. One study reported some better preservation of residual urine production [145], and in another small retrospective analysis better preservation of residual creatinine clearance was found in APD patients [150]. Confirmation of these unexpected findings is required.

The use of icodextrin has effects on some laboratory investigations. All studies have shown a decrease of plasma sodium of on average 3 mmol/L. It is likely to be caused by the increased plasma maltose concentrations, as a compensatory mechanism to avoid hyperosmolality. A significant discrepancy has been reported between glucose measurements using glucose dehydrogenese-based methods and methods obtained in the laboratory using a reference method, like hexokinase [151, 152]. These methods overestimate plasma glucose levels due to the presence of oligosaccharides (mainly maltose) in the circulation and are therefore unsuitable for use in patients on icodextrin.

Dialysis with icodextrin also interferes with the measurement of plasma amylase activity resulting in a reduction of amylase levels. Plasma amylase activity may be reduced by 90% [153, 154]. Consequently, because icodextrin does not affect lipase activity, lipase measurement should be used for the diagnosis of suspected pancreatitis in dialysis patients on icodextrin. Skin rashes are the most frequent side effect of icodextrin [144]. Their prevalence varies from 0–6% to 15% [155–157]. An incidence of 1 per 60 patients-years has been found in a large post-marketing survey [158]. The occurrence is not related to the presence of circulating dextran antibodies [159]. The rash is usually not severe and is self-limiting.

An epidemic of culture-negative peritonitis in icodextrin patients was first described in 1999 [160]. It was followed by many other reports [161–165]. The incidence peaked in spring 2002. It appeared to be due to contamination by peptidoglycans, which are components of the bacterial cell wall [166]. The problem disappeared after adjustment of the production process, leading to peptidoglycan levels below the detection limit. It should be appreciated, however, that peritoneal effluent cell counts in stable patients are higher on icodextrin than on glucose-based conventional solutions [167]. The meaning of this is unknown.

The Place of Icodextrin in Modern Peritoneal Dialysis

The use of icodextrin for the long dwell both in CAPD and APD is well established because of its superior ultrafiltration profile and reduced exposure to glucose and glucose degradation products. A skin rash is the most important side effect, but it is usually mild and its occurrence is relatively rare. It should, however, be appreciated that plasma sodium levels are on average 3 mmol/L lower compared to glucose and that a low plasma amylase activity is present. Self-assessment methods for blood glucose determinations will have to be checked for interference of maltose. When these precautions are taken into account, icodextrin is currently the preferred osmotic agent for the long dialysis dwells.

Mixing icodextrin with other osmotic agents, for instance, a small amount of glucose, has been investigated [168–170], but this solution has not been taken into production. More recently, an experimental solution consisting

of 6.8% icodextrin, 2.86% glucose, and a sodium concentration of 121 mmol/L reported superior ultrafiltration and sodium removal during a 15-h dwell, but its applicability is not known [171]. The use of icodextrin in a glucose and amino acids mixture has been investigated in short APD dwells and was associated with only moderate increases in plasma levels of icodextrin metabolites, while leading to a marked reduction in the absorption of glucose [172]. However, this approach is also experimental.

Biocompatible PD Solutions

The bioincompatibility of conventional PD solutions, as discussed in Chapter 27, has led to the development of dialysis solutions that were different in one or more of the following: buffer, pH, and glucose degradation products (GDPs). No changes were made in the concentrations of glucose. The rationale for focusing on buffer, pH, and GDPs lies in the results of in vitro biocompatibility studies. The most important ones have been summarized in [173]. The combination of a low pH with lactate caused a partly irreversible decrease of the intracellular pH [174]. Heat sterilization of dialysis solutions leads to the formation GDPs and to marked toxicity of cultured mouse fibroblasts [175]. GDPs consist of aldehydes and dicarbonyl compounds [176], of which 2,3-dideoxyglucosone might be the most toxic one. They also promote the formation of advanced glycosylation end products at a faster rate than glucose itself.

Based on the above considerations, four dialysis fluids have been developed and are available in Europe and parts of Asia. These are Trio® (Gambro), Physioneal® (Baxter), Balance® (Fresenius), and Bicavera® (Fresenius). Their characteristics are summarized in Table 11.3. The reduction in the content of GDPs and the use of bicarbonate as a buffer can only be achieved by the use of dialysis bags with two compartments, which are mixed just before inflow. To reduce the formation of GDPs, glucose should be sterilized at a low pH, e.g., pH = 3, and in a high concentration. In Trio® and Balance®, glucose is sterilized separately.

It is evident from Table 11.3 that the solutions are different with regard to pH and buffer. The amount of GDP is somewhat higher in Physioneal®, but still less than half of that in Dianeal®. When bicarbonate only is used as a buffer, supraphysiological concentrations (35–40 mmol/L) are required. In vitro studies, however, showed no adverse effect of this excess [133, 177–180] with the exception of one [181]. The results with the bicarbonate buffer were similar to those obtained with lactate after adjustment to a normal pH [178].

In Vitro -and Animal Studies

All biocompatible solutions showed superiority in in vitro studies, when compared with conventional PD solutions [133, 177–180, 182–185]. This has also been shown for their effects on cultured mesothelial cells, where the bicarbonate buffer did better than the lactate buffer [186]. The in vitro studies have been reviewed in [180, 187, 188].

Animal studies have mainly focused on direct effects of exposure on peritoneal vessels, on changes in imprints of liver mesothelium, and on effects of long-term exposure of the peritoneal membrane. Intravital microscopy of mesenteric vessels in the rat showed that a conventional 4.25% glucose dialysis solution induced maximal vasodilation of mesenteric arteries, resulting in doubling of the arterial flow [189]. A reduction in the bicarbonate content reduced this effect, and it was absent when a bicarbonate buffer was used. The same model was used to study leukocyte recruitment [190]. The inhibition of lipopolysaccharide (LPS)-stimulated recruitment by conventional PD fluids was lower when Bicavera® was used.

Replacement of lactate by bicarbonate caused less damage of murine liver mesothelial cells [191], but this was not confirmed in trypsin washout experiments in a rabbit model [192]. The presence of GDPs in the dialysis solution caused marked mesothelial toxicity after 10 weeks exposure [193]. Exposure of Physioneal® in rats for 12 weeks showed a reduction in the peritoneal content of advanced glycosylation end-products (AGE), but not in peritoneal pentosidine [194]. Morphological changes after 10 weeks exposure in rats also showed a reduction in angiogenesis [195]. This

Table 11.3 Characteristics of biocompatible PD solutions

	pH	Buffer	3-DG (μmol/L)	Source
Trio	6.3	Lactate	65	Gambro
Physioneal	7.4	Bicarbonate/lactate	253	Baxter
Balance	7.0	Lactate	–	Fresenius
Bicavera	7.4	Bicarbonate	42	Fresenius

3-DG: 3-desoxyglycosone

reduction in the number of vessels by Physioneal® was even 50% after exposure for 20 weeks [196]. In the latter study, less peritoneal fibrosis was also found. A lower number of peritoneal vessels and a reduction in peritoneal fibrosis, in combination with a reduction in the staining for endothelial nitric oxide synthase (eNOS), vascular endothelial growth factor (VEGF), picosirius red (stains fibrillary collagen), and AGE have later been confirmed, together with less mesothelial damage on Physioneal® [197]. The results of various animal studies have been reviewed in [198]. It can be concluded that the animal studies, also after long-term exposure, showed superiority in the preservation of peritoneal morphology and function of the biocompatible PD solutions compared to the conventional ones.

Ex Vivo Studies

Ex vivo studies have focused on functions of macrophages isolated from peritoneal effluent, on the properties of mesothelial cells cultured from the dialysate, and on substances that can be determined in effluent and that reflect some properties of peritoneal tissues. Peritoneal macrophages isolated after a 30 min dwell showed impaired secretion of tumor necrosis factor alpha (TNF-α) on conventional lactate buffered solutions [199]. This was unchanged after isolation from a bicarbonate solution but improved after a dwell with a bicarbonate/lactate fluid. Treatment with Physioneal® for 6 months resulted in a sustained improvement in peritoneal macrophage function [200]. The use of Balance® led to a reduction of epithelial-to-mesenchymal transition of mesothelial cells cultured from effluent when compared with a conventional solution [201].

Biocompatible dialysis solutions when used in prevalent patients have all been associated with an increase in the CA 125 concentration in effluent. This has been shown for Trio® [202], Physioneal® [203], Balance® [201, 204], and Bicavera® [205]. It is remarkable that these solutions, which are different with regard to buffer and pH, all show this phenomenon, suggesting an increase in mesothelial cell mass [137]. The data could be interpreted as a consequence of the reduced amount of GDPs present in all solutions, but this is still speculative.

Some studies showed a decreased effluent concentration of hyaluronan [202–204] while treated with biocompatible solutions. This substance has been suggested as a marker of inflammation and tissue remodeling in the peritoneal cavity. The results of studies of dialysate procollagen peptides have been equivocal [202, 203]. No consistent effects were found for effluent VEGF.

Clinical Studies

Clinical studies with biocompatible PD solutions have focused on inflow pain, correction of acid/base balance, effects on peritoneal transport, serum levels of AGEs, and whether or not an effect on residual renal function and patient survival is present.

A reduction of inflow pain on biocompatible solutions has been reported, which was statistically significant for Physioneal® [206] and just did not reach significance for Trio® [202]. This effect is likely to be due to the higher pH compared to conventional lactate buffered solutions [202]. The effect of a pure bicarbonate-based solution was less pronounced [206].

Replacement of lactate by bicarbonate resulted in a small increase in plasma bicarbonate in adult CAPD patients [207] and also in children treated with Bicavera® [205]. It appeared that the net bicarbonate gain was dependent on the ultrafiltration rate, plasma bicarbonate, and the bicarbonate content of the dialysis solution [208]. A comparison of a bicarbonate/lactate buffer with bicarbonate showed no differences in plasma bicarbonate or lactate concentrations [209, 210]. A randomized controlled clinical study comparing Physioneal® with the conventional solution showed that both solutions were equivalent with regard to plasma bicarbonate level and peritoneal solute transport [211]. A somewhat better ultrafiltration and a lower peritonitis incidence were also reported in that study, but these data have not been confirmed in other studies [212]. In general, no marked acute effects on peritoneal transport are present [213].

Glucose degradation products are low-molecular -weight solutes that are almost completely absorbed during a dialysis dwell. As stated above, GDPs lead to the formation of AGEs at a faster rate than glucose itself. It is therefore interesting that some clinical studies reported a reduction in the serum concentration of some AGEs while on biocompatible solutions. This has been described for total AGE and carboxymethyllysine in patients on TRIO® [214], and for imidazolone and carboxymethyllysine in the Eurobalance trial [204]. However, the decreases are small and the clinical relevance is unknown.

An unexpected effect of Balance® was found on residual renal function, which was better preserved than with the control solution [204]. These results will have to be confirmed to be sure that this effect has not been caused by chance. Another unexpected finding comes from the retrospective analysis done in Korea, where patient survival on Balance® was reported to be higher compared to treatment with conventional dialysis solutions [215]. However, the study has some methodological flaws, making the interpretation difficult. Obviously, more studies are required.

The Place of Biocompatible Solutions in Modern Peritoneal Dialysis

In vitro data, animal studies, and ex vivo data have shown beneficial effects of solutions with a reduced content of GDPs, often in combination with a higher pH and the inclusion of bicarbonate as a buffer. Clinical studies have not shown inferiority compared to the conventional solutions, and have shown some benefits, like less pain on infusion and lower serum levels of advanced glycosylation end products. It is noteworthy that, at present, the authors are not aware of any patient who developed encapsulating peritoneal sclerosis after treatment with biocompatible solutions exclusively. However, the results of more long-term studies will have to be known before determining their place in routine peritoneal dialysis.

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